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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary Examiner		Application No.	Applicant(s)					
Bruce D. Hissong, Ph.D. 1646 - The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION. Eastment of time may be available as under the provision of 30° Fch112661, in so event flower, may raply be strewly field If NO period for right is specified above, the maintain statistic propriets will apply and will expire 3X (8) MONTHS from the mailing date of this communication. Fashis to lesson as AshnotNeel 103 U.S. S. § 133). Any right received by the Office tour than time on maintain statistic maintain glass of this communication. Fashis to lesson as AshnotNeel 103 U.S. S. § 133). Any right received by the Status 1) Separation of Status 1) Responsive to communication(s) filled on 05 March 2007. 2a) This action is FINAL. 2b) This action is non-final. 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213. Disposition of Claims 4) Claim(s) 1-15 is/are pending in the application. 4a) Of the above claim(s) 7-13 is/are withforwarn from consideration. 5] Claim(s) is/are allowed. 6) Claim(s) is/are allowed. 6) Claim(s) is/are allowed. 6) Claim(s) is/are allowed. 7) Claim(s) is/are allowed. 8) The specification is objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to See 37 CFR 1.121(d). 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152. Priority under 35 U.S.C. § 119 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a) (d) or (f). 3) All b) Some c) None of the priority documen		10/825,382	LIU ET AL.					
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DETAILED ACTION

Formal Matters

- 1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Bruce D. Hissong, Art Unit 1646.
- 2. The Applicants' response to the office action mailed on 12/4/2006 was received on 3/5/2007 and has been entered into the record.
- 3. Claims 1-15 are currently pending, with claims 7-13 withdrawn as non-elected subject matter, and claims 1-6 and 14-15 the subject of this office action.

Priority

The Applicants' amendment to remove a claim to the benefit of co-pending U.S. Application No. 09/910,406, filed 7/19/2001, to U.S. Provisional Application No. 60/219.128, filed 7/19/2000, and to Japanese Application No. 317160, filed 10/17/2000, is noted. Accordingly, the earliest effective filing date of the instant application has been determined to be 3/10/2004, which is the filing date of U.S. Provisional Application No. 60/552,279.

Information Disclosure Statement

The information disclosure statements received on 1/3/2007 and 3/5/2007 have been fully considered.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejections maintained/new grounds of rejection

1. Claims 1-2, 4-6, and 14-15 <u>remain rejected</u>, and dependent claim 3 is also rejected, under 35 USC § 112, first paragraph, regarding lack of enablement for a method of increasing the IL-10/IFN- γ ratio in a subject, wherein said method comprises oral administration of any IFN- τ isoform other than those set forth in SEQ ID NOs 2 or 3, as set forth on pages 2-4 of the prior office action mailed on 12/4/2006.

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In the response received on 3/5/2007, the Applicants argue that the claims recite administration of a dose of IFN- τ of greater than 5 x 10^8 units, rather than, for example, milligrams. The Applicants also assert that the specification teaches that an IFN- τ dose of 5 x 10^8 units has a specific activity of about 1 x 10^8 antiviral units/ml protein, which achieves the desired therapeutic effect. Furthermore, the Applicants argue that the antiviral activity for any IFN- τ isoform can be ascertained using standard *in vitro* cytopathic assays. For these reasons, the Applicants believe that a person of ordinary skill in the at would be able to orally administer IFN- τ at a dose of greater than 5 x 10^8 units without further, undue experimentation.

These arguments have been fully considered and are persuasive in that the Examiner agrees that a person of ordinary skill in the art could ascertain the activity of an IFN-τ isoform and administer a dose of greater than 5 x 10⁸ units. However, it is noted that the specification teaches that IFN-τ, refers to any one of a family of proteins having at least one of several possible characteristics, including having about 45-68% homology to IFN- α sequences and greater than 70% homology to known IFN-t sequences (page 7, paragraph 0038). Furthermore, the specification, on page 8, paragraph 0039, also teaches that an ovine IFN- τ protein is one having about 80%, more preferably 90%, sequence homology to the sequence identified by SEQ ID NO: 2. Thus, the breadth of the claims is excessive because the claims read on methods of administering any protein with 70% or greater homology to known IFN-τ seguences, including molecules with at least 80% homology to the protein of SEQ ID NO: 2, and also including any ovine or bovine IFN-τ polypeptide. There is no guidance or examples in the specification that teach that any IFN-τ with less than 100% homology to SEQ ID NO: 2 or 3 can be orally administered to a subject, resulting in an increase in the IL-10/IFN-γ ratio. A person or ordinary skill in the art would not be able to predict which of the many possible polypeptide sequences with less than 100% homology to SEQ ID NO: 2 or 3 would be able to increase the IL-10/IFN-y ratio, and thus be used commensurate in scope with the claims.

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In summary, due to the excessive breadth of the claims, which read on a method of administering any IFN- τ polypeptide, peptide, or fragment thereof, the lack of guidance or examples in the specification which teaches administration of any polypeptide with less than 100% homology to SEQ ID NO: 2 or 3, and unpredictability in the art regarding the effects of such polypeptides, a person of ordinary skill in the art would require further, undue experimentation to make and use any IFN- τ polypeptide, other than those of SEQ ID NO: 2 or 3, in a method of increasing the IL-10/IFN- γ ratio in subject. Finally, it is noted that claim 3 is rejected for depending from a rejected base claim.

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2. Claims 1-6 and 14-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of achieving a desired clinical endpoint by increasing the IL-10/IFN-γ ratio in a subject suffering from an autoimmune disorder, wherein the disorder is multiple sclerosis, does not reasonably provide enablement for achieving a desired clinical endpoint by increasing the IL-10/IFN-y ratio in a subject suffering from any other autoimmune disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The breadth of the claims is excessive because the claims read achieving a desired clinical endpoint with any autoimmune disorder. While the specification provides guidance and examples showing orally administered IFN-τ of SEQ ID NO:3 results in an increase in the IL-10/IFN-y ratio in multiple sclerosis patients, and teaches that oral administration of the protein of SEQ ID NO: 3 is effective in treating multiple sclerosis, there is no guidance or examples that teach that a desired clinical endpoint may be achieved in any other autoimmune disease can by oral administration of the polypeptide of SEQ ID NO: 3 or any other IFN-τ polypeptide. A person of ordinary skill in the art would know that autoimmune disorders encompass a wide range of diseases, both organ-specific and systemic, whose etiologies and pathogenesis are not fully known but are understood to be influenced by multiple factors, including genetic and environmental influences (see specification, paragraphs 0108-0111). Thus, the skilled artisan would not be able to predict which of the many possible autoimmune disorders would respond favorably to increasing the IL-10/IFN-γ ratio by oral administration of IFN-τ, thus achieving a desired clinical endpoint. For example, would type I autoimmune/hypersensitivity reactions, which are known to be associated with Th2 responses, be treatable by a method to increase the IL-10/IFN-y ratio? For these reasons, it would require

further, undue experimentation on the part of a person of ordinary skill in the art to determine which autoimmune disease could be treated by orally administered IFN- τ , wherein a desired clinical endpoint is achieved.

In summary, due to the excessive breadth of the claims, which read on methods for increasing the IL-10/IFN- γ ratio in a subject suffering from any autoimmune disease by orally administering IFN- τ , the lack of guidance and examples in the specification showing that a desired clinical endpoint can be achieved in any disease other than multiple sclerosis by orally administered IFN- τ , and the unpredictability inherent in the invention regarding which diseases can be treated, a person of ordinary skill in the art would require further, undue experimentation to determine which autoimmune diseases will favorably respond to an orally administered IFN- τ -stimulated increase in the IL-10/IFN- γ blood ratio.

Claim Rejections - 35 USC § 112, first paragraph - written description

New grounds of rejection

Claims 1-6 and 14-15 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to oral administration of IFN- τ polypeptides. As discussed in the above 35 U.S.C. 112, first paragraph enablement rejection #1, the specification states that IFN- τ proteins can include any ovine or bovine IFN- τ protein, or any protein with at least 70% homology to a known IFN- τ protein, or at least 80% homology to the proteins of SEQ ID NO: 2 or 3. The claims do not require the IFN- τ of the instant invention to have any particular structure other than to have at least 70% amino acid homology to any IFN- τ polypeptide. The specification does not teach what deletions, additions, or substitutions can be made in an IFN- τ polypeptide, resulting in a protein that is at least 70% homology to any known IFN- τ protein, and there is no disclosure of any particular region of any IFN- τ polypeptide, from any species, that must be conserved in order to maintain the desired biological function. Thus, the Applicants

have not fully described the genus of IFN- τ polypeptides capable of increasing the IL-10/IFN- γ ratio, and thus capable of being used commensurate in scope with the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the IFN- τ proteins have at least 70% homology to any known IFN- τ protein. There is no identification of any particular portion of an IFN- τ polypeptide that must be conserved in order to maintain the desired biological activity (i.e. the ability to increase the IL-10/IFN- γ ratio). Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of claims 1-6 and 14-15 under 35 USC § 112, second paragraph, regarding missing essential method steps, as set forth on pages 3-4 of the prior office action mailed on 12/4/2006, is withdrawn in response to Applicants' arguments that there is no need to measure the serum IL-10 levels before or after IFN- τ administration because the recited dose will increase serum IL-10 levels. This argument has been found persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soos *et al* (WO 97/33607), in view of van Boxel-Dezaire *et al* (*Ann. Neurol.*, 1999, Vol. 45, p. 695-703), and further in view of Petereit *et al* (J. Neurol. Sci., 2003, Vol. 206, p. 209-214), all of which were cited in the information disclosure statement received on 5/5/2004.

The claims of the instant invention are drawn to methods of increasing the IL-10/IFN- γ ratio in subjects suffering from an autoimmune disease or viral condition, wherein said method comprises oral administration of IFN- τ at a daily dose of 5 x 10⁸ units or greater. The claims are further drawn to administration of ovine or bovine IFN-t, and specifically that of SEQ ID NO: 2 or 3, and specifically for the treatment of multiple sclerosis.

Soos *et al* teach oral administration of IFN- τ polypeptides for the treatment of multiple sclerosis (see abstract; p. 5, lines 8-21; p. 11, line 5 – p. 12, line 16, p. 23, Example 1; and all claims). Specifically, Soos *et al* teaches administration of IFN- τ defined by SEQ ID NO: 2, which exhibits 100% homology to the polypeptide defined by SEQ ID NO: 2 of the instant application (see sequence comparison 1). Soos *et al* also teaches that other autoimmune disorders, including type I diabetes mellitus, lupus erythematosus, Crohn's disease, rheumatoid arthritis, and psoriasis, can also be treated by orally administered IFN- τ (p. 11, lines 17-21), and further teaches that orally administered IFN- τ increases serum IL-10 levels (p. 26, Example 5), while promoting stable of decreasing IFN- γ blood levels (p. 2233-2234, Figure 2), thus resulting in an overall increase in the IL-10/IFN- γ ratio. Furthermore, Soos et al teaches combination therapies wherein IFN-t is co-administered with other therapeutic agents effective for the treatment of multiple sclerosis (p. 20, line 19 – page 21, line 14). Soos *et al* is silent regarding oral administration of IFN- τ at doses of at least 5 X 10⁸ units/day.

van Boxel-Dezaire *et al* teaches that multiple sclerosis is characterized by decreased IL-10 levels (see Figures 1-3), and suggests that IL-10 plays an important role in the control of disease progression. Petereit *et al* teach that multiple sclerosis patients with higher IL-10 secretion had lower clinical disability scores than patients with lower IL-10 secretion (see abstract and p. 211-212).

Therefore, it would have been obvious to a person of ordinary skill in the art, at the time the instant invention was made, to combine the teachings of Soos *et al* with those of van Boxel-Dezaire *et al* and Petereit *et al* to orally administer IFN- τ to increase the IL-10/IFN- γ ratio in order to treat autoimmune disease such as multiple sclerosis. Soos *et al* provides the motivation to treat multiple sclerosis, and other autoimmune disorders, with orally administered

IFN-τ. Petereit *et al* and van Boxel-Dezaire *et al* provide the motivation to increase the production of IL-10, and to increase the IL-10/IFN- γ ratio in multiple sclerosis. Furthermore, by teaching that IL-10 secretion is increased after oral IFN- τ administration, Soos *et al* provides further motivation to use orally administered IFN- τ , and by showing that IFN- γ levels or unchanged or decreased after IFN- τ administration, also provides a reasonable expectation of success by insuring that the IL-10 levels, and therefore IL-10/IFN- γ ratios, would be increased in the treated patients.

Although Soos et al does not specifically teach oral administration of IFN- τ at doses of at least 5 X 10⁸ units/day, a person of ordinary skill in the art would be motivated to optimize the dosage required for effective treatment. Furthermore, because Soos *et al* teaches that IFN- τ treatment is not associated with the toxicity associated with administration of other IFNs (p. 12, line 26 – p. 13, line 4), the skilled artisan would be assured that the dosage optimization would likely not harm the patient. Additionally, while Soos *et al* does not specifically teach administration to the intestinal tract of a subject, such methods are well-known in the art and would be within the skilled artisan's abilities. Finally, Soos *et al* teaches that cessation of oral IFN- τ administration results in a relapse of clinical symptoms (p. 26, Example 6), providing the motivation for the skilled artisan to continue administration during the period the patient exhibits symptoms until the desired clinical endpoint, a reduction in symptoms, is reached.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with

this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Rejections withdrawn

1. Rejection of claims. 1-6 and 14-15 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent 7,083,782, as set forth on pages 4-7 of the office action mailed on 12/4/2006, is <u>withdrawn</u> in response to Applicants' submission of a terminal disclaimer.

New grounds of rejection

2. Claims 1-6 and 14-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following claims in the indicated applications:

Application No.	<u>Claims</u>
10/825,068	1, 3, 6, 8, 10-11
10/825,457	1-6
11/040,706	1-6, 25
10/884,741	1-4, 8-10, 19-22
11/112,369	1, 17, 18

Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims of the applications cited above are drawn to methods of oral administration of IFN- τ at a dose of 5 x 10⁸ units or greater. The claims of the instant application do not identify a population for treatment, and thus the claims read on administration of IFN- τ to all possible subjects. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of orally administering IFN- τ in the same dosage as specified in the instant application, are the same regardless of whether the purpose is to stimulate IL-10 production, prevent IFN- γ production, or stimulate any other

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biological activity (Ex parte Novitski, 26 USPQ 1391). The instant method steps of oral

administration of IFN- $\!\tau$ would inherently perform these activities.

This is a <u>provisional</u> obviousness-type double patenting rejection because the conflicting

claims have not in fact been patented.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application

or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH Art Unit 1646

OBERT S. LANDSMAN, PH.D.

SEQUENCE COMPARISON 1

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RESULT 3
AAW31698
TD
     AAW31698 standard; protein; 172 AA.
XX
AC
     AAW31698;
XX
DT
     14-APR-1998 (first entry)
XX
DE
     Mature ovine interferon-tau (OvIFNtau) protein.
XX
     Interferon-tau; ovine; human; auto immune disease; treatment; toxicity;
KW
     IFN tau; multiple sclerosis; diabetes mellitus; asthma; allergy; cancer.
KW
ХX
     Ovis aries.
OS
XX
PN
     WO9733607-A1.
XX
PD
     18-SEP-1997.
XX
PF
     12-MAR-1997;
                    97WO-US003794.
XX
PR
     15-MAR-1996;
                    96US-00616904.
XX
PA
     (UYFL ) UNIV FLORIDA.
XX
PΙ
     Soos JM, Schiffenbauer J, Johnson HM;
XX
DR
     WPI; 1997-470642/43.
     N-PSDB; AAV02288.
DR
ХX
PT
     Oral administration of interferon-tau for treatment of auto-immune
PT
     disease - avoids toxicity of interferon alpha and generates fewer
рψ
     specific antibodies than injection.
XX
PS
     Claim 5; Page 31; 48pp; English.
XX
CC
     This is a mature ovine interferon-tau (OVIFNtau) protein. The ovine and
CC
     the human interferon-tau (IFN tau) can be used in the treatment of
CC
     mammalian diseases responsive to IFN tau. The new feature in the
CC
     treatment is that IFN tau is administered orally. The method is used to
CC
     treat immune, particularly autoimmune disease, specifically multiple
CC
     sclerosis (a preferred application, reducing both severity and frequency
     of relapses), type I diabetes mellitus, lupus erythematosus, amyotrophic
CC
CC
     lateral sclerosis, Crohn's disease, rheumatoid arthritis, stomatitis,
CC
     asthma, allergies and psoriasis, particularly in humans or dogs. IFN tau
CC
     is also useful for treating cancer (e.g. hairy cell leukaemia, Kaposi's
CC
     sarcoma and multiple myeloma), cell proliferation and viral diseases
CC
     (hepatitis, human immunodeficiency virus etc., including prevention of
CC
     maternal transmission). It is also used for increasing fertility in
CC
     female mammals (increasing life time of the corpus luteum). Oral
CC
     administration is as effective as injection but is more convenient and
CC
     generates a lower level of anti-IFN tau antibodies. Use of IFN tau avoids
CC
     the toxicity associated with use of IFN alpha
XX
     Sequence 172 AA;
SQ
  Query Match
                          100.0%; Score 907; DB 2; Length 172;
  Best Local Similarity 100.0%; Pred. No. 1.3e-92;
  Matches 172; Conservative 0; Mismatches
                                                 0; Indels
```

0; Gaps

Qy	1	CYLSRKLMLDARENLKLLDRMNRLSPHSCLQDRKDFGLPQEMVEGDQLQKDQAFPVLYEM 60
Db	1	CYLSRKLMLDARENLKLLDRMNRLSPHSCLQDRKDFGLPQEMVEGDQLQKDQAFPVLYEM 60
Qу	61	LQQSFNLFYTEHSSAAWDTTLLEQLCTGLQQQLDHLDTCRGQVMGEEDSELGNMDPIVTV 120
Db	61	LQQSFNLFYTEHSSAAWDTTLLEQLCTGLQQQLDHLDTCRGQVMGEEDSELGNMDPIVTV 120
Qy	121	KKYFQGIYDYLQEKGYSDCAWEIVRVEMMRALTVSTTLQKRLTKMGGDLNSP 172
Db	121	KKYFQGIYDYLQEKGYSDCAWEIVRVEMMRALTVSTTLQKRLTKMGGDLNSP 172

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